Department of Pesticide Regulation

Paul E. Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

TO: Denise Webster
Pesticide Registration Specialist HSM-01007
Pesticide Registration Branch

FROM: Thomas Thongsinthusak **[Original signed by T Thongsinthusak]**
Staff Toxicologist (Specialist)
(916) 445-4267

DATE: July 12, 2001

SUBJECT: BRAND NAME: Tamaron
ACTIVE INGREDIENT: Methamidophos
COMPANY NAME: Bayer Corporation
TRACKING I.D. NUMBER: 189659
RECORD NUMBER (RN): 181706
DATA PACKAGE NUMBER (DPN): 315-165
EPA REGISTRATION NUMBER: 3125---
TITLE: A Dermal/Intravenous Cross Over Study to Determine the Dermal Absorption of [^{14}C]-Methamidophos in Male Rhesus Monkeys
(Revised the July 3, 2001 memo by adding the tracking I.D., RN and DPN. There are no other changes)

Sierra Biomedical, Incorporated (SBi) conducted a dermal absorption study of methamidophos in four male rhesus monkeys (Fuller, 2000). This study was completed on August 12, 2000. All aspects of this study performed at the SBi were conducted in accordance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160), except for a few protocol deviations. For example, urine containers did not contain dry ice when checked at approximately 18 hours following the intravenous (IV) administration and the apparatus used to protect the dermal-dose area of the back of two of the animals became dislodged within 1 and 2 hours after dosing. These deviations could affect the results of the study. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Preparation of Test Subjects

Basically, the method of the study was based on the principle used by Feldmann and Maibach (1974) or Wester and Maibach (1985). Four male rhesus monkeys, experimentally naive and weighing 4.6 to 5.5 kg (average 5.1 kg) at the outset of the study, were used in this study. Prior to the dermal or intravenous administration, the animals were placed in restraint chairs and were kept in the chairs for 8 hours following dosing. The animals were then transferred to metabolism cages. The same four monkeys were used for the dermal administration of the dose. Fourteen days after the initiation of the IV dosing phase and on the day prior to the dermal administration, an area on the back of the animals, large enough to accommodate a Duoderm® patch and a protective dome, was shaved. The shaved area was cleaned with Ivory soap solution (1:100, v/v,

with distilled water) and patted dry. On the day of the dermal dose administration, a Duoderm® patch was placed around the dosing site to expose a 4 x 6-cm area.

B. Preparation and Administration of the Dose

[$^{14}CH_3S$]-Methamidophos was prepared in 0.9% saline for IV dosing and [$^{14}CH_3S$]-Tamaron 600 SL for dermal dose administration. For the IV dose administration, four male monkeys received a mean dose of 239 ± 2 µg of [$^{14}CH_3S$]-methamidophos in 1 mL of 0.9% saline via an IV bolus injection through a catheter in a cephalic vein. The mean dose was 46.9 µg/kg body weight.

Before the dermal dose administration, the four animals were placed in the restraint chairs and received a dermal application of 0.1 mL of [$^{14}CH_3S$]-Tamaron 600 SL. The mean dose was 239 ± 2 µg of test substance equivalent approximately to 10 µg/cm^2. The application site was covered with a nonocclusive dome and secured. Approximately 8 hours after dosing, the animals were removed from the chairs and the protective dome and Duoderm® patch were removed. The surface of the treated site was swabbed with a series of 16 soap-water soaked cotton-tipped swabs (1% Ivory liquid soap in water) followed by two isopropyl alcohol (IPA)-wetted swabs. Approximately 24 and 48 hours after dose administration, the entire dose site was swabbed with two IPA-wetted swabs. After swabbing, an area of the dose site (approx. 4 x 1.5-cm), representing ¼ of the dose site) was tape stripped 16 times. A separate area of the dose site was used for the tape stripping each day. On study day 19, a final series of two IPA-wetted swabs was used to swab the dose site.

C. Sample Collection and Analysis

Urine and feces (including feed biscuits) were collected at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours after the IV dosing. Blood samples were collected at 5 min., 15 min., and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dosing. Other samples collected for analysis were IV dose catheters, dosing syringes and needles, excreta, plasma, and red blood cells.

For the dermal dose administration, urine, feces and feed biscuits were collected at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours. Blood samples were collected at 15 min., and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dosing. Other samples collected for analysis were dermal application pipettes, swabs, tape strips, Duoderm® patches, protective (dermal) domes, excreta, plasma and red blood cells.

D. Results

For IV dosing, an average of 11.35% of the administered dose was recovered in the urine and 0.51% was recovered in the feces, indicating that the main route of excretion was through the urine. Results of cumulative urinary excretion are shown in Table 1.

Table 1. Cumulative urinary excretion of the applied dose in rhesus monkeys following the intravenous bolus dose of [$^{14}CH_3S$]-methamidophos at 46.9 μg/kg body weight.

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	8.22	8.22
4-8	1.84	10.06
8-12	0.28	10.34
12-24	0.38	10.72
24-48	0.22	10.94
48-72	0.19	11.13
72-96	0.12	11.25
96-120	0.10	11.35

For dermal administration, the majority of the applied dose (57.3%) was recovered in the skin swabs with soap and water. Alcohol swabs contained 4.10% and tape strips contained 0.15% of the administered dose. Other dose recoveries were: Duoderm® 2.76%, dermal dome 1.33% and feed biscuits 0.11%. The mean total recovery of unabsorbed dose was 65.75%. The mean recovery in the urine was 1.20% and that in the feces was 0.06%. Results of urinary excretion are shown in Table 2.

Table 2. Cumulative urinary excretion of the applied dose in rhesus monkeys after the dermal administration of [$^{14}CH_3S$]-methamidophos at 10 μg/cm^2.

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	0.04	0.04
4-8	0.08	0.12
8-12	0.09	0.21
12-24	0.33	0.54
24-48	0.29	0.83
48-72	0.17	1.00
72-96	0.11	1.11
96-120	0.09	1.20

Determination of the dermal absorption of methamidophos is based on the principle used by Feldmann and Maibach (1974) or Wester and Maibach (1985). The method employs the percentage of the applied dose excreted in the urine or feces or both obtained from topical administration and IV dosing. Since the majority of the administered dose was excreted in the urine, only the dose recovered in the urine is used for estimation of the dermal absorption.

The estimated maximum urinary excretion following both routes of administration was used so that there was no discrepancy for the length of sample collection times. The estimated maximum excretion of the dose in the urine was performed by using the exponential saturation model with lag time (Thongsinthusak *et al.*, 1999). The scientific software Systat®, version 8.0 (SPSS, 1998) was utilized for the statistical analysis and plotting a graph. The estimated maximum excretion post IV dosing was determined to be 11.09% and that for post dermal dosing was determined to be 1.25% (Figure 1).

The dermal absorption was calculated using the equation shown below.

$$\% \text{ Dermal absorption} = \frac{(\text{Topical})\ ^{14}\text{C in urine (\% dose)}}{(\text{IV})\ ^{14}\text{C in urine (\% dose)}} \times 100$$

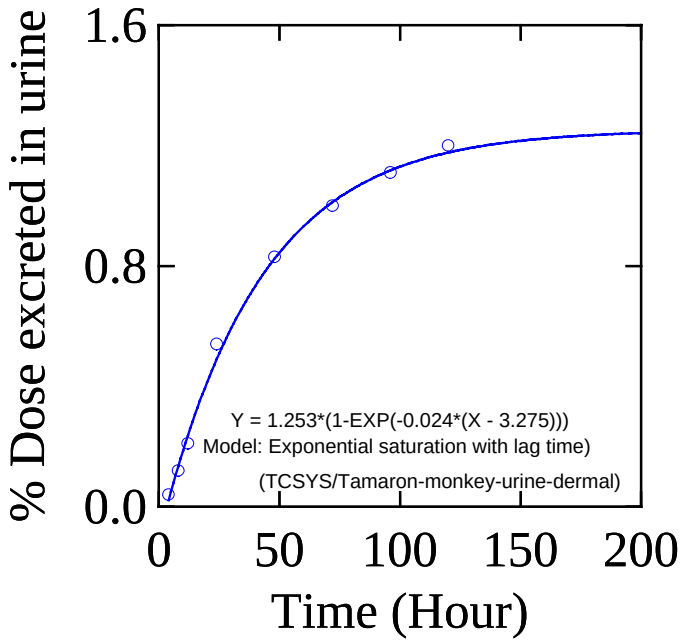
$$\% \text{ Dermal absorption of methamidophos in monkeys} = \frac{1.25}{11.09} \times 100 = 11.3\%$$

E. Discussion and Conclusion

[^{32}P]-Methamidophos is ideal for use in a dermal absorption study in animals because it is radiolabeled at the core of the molecule. Loss of radioactivity due to volatilization of its metabolites is expected to be minimal. However, [$^{14}CH_3S$]-methamidophos was used in this study. The dermal dose used in this study was higher than anticipated. The low end of the dermal dose should range from 1 to 6 $\mu g/cm^2$. The dermal absorption of 11.3% was estimated based upon the conditions of this study. However, this dermal absorption value is not recommended for the exposure assessment of methamidophos because the mean recovery following the IV administration was very low, indicating the loss due to volatile metabolites.

DPR recommends a new dermal absorption study be conducted by using ^{32}P-methamidophos in animals, such as nonhuman primates. In a dermal absorption study, it is essential that a compound be radiolabeled at a position, which is part of the core of the molecule. An appropriate dermal dose should be prepared in an aqueous suspension with the addition of formulation blank (ingredients used in the methamidophos formulation minus methamidophos). A probe study is recommended. A dermal absorption study protocol should be submitted to DPR for review prior to the study.

Figure 1. Asymptotic plot of cumulative urinary excretion of [$^{14}CH_3S$]-methamidophos after dermal administration of 10 µg/cm^2 to rhesus monkey skin.



SYSTAT Rectangular file
D:\DATA\TCSYS\Tamaron-monkey-urine-Dermal.SYD,
created Mon Jun 25, 2001 at 16:09:17, contains variables:

Iteration

No.	Loss	MAX	RATE	LAG
0	.174620D+01	.400000D+00	.102000D+00	.103000D+00
1	.744210D+00	.662309D+00	.423484D-01	.355696D+01
2	.197804D+00	.877757D+00	.513890D-01	.415829D+01
3	.815821D-01	.987012D+00	.438029D-01	.445018D+01
4	.394357D-01	.105788D+01	.385910D-01	.451215D+01
5	.219025D-01	.110654D+01	.348462D-01	.443948D+01
6	.135097D-01	.114228D+01	.320680D-01	.428919D+01
7	.905929D-02	.117028D+01	.299317D-01	.410069D+01
8	.657270D-02	.119353D+01	.282279D-01	.389906D+01
9	.518570D-02	.121385D+01	.268168D-01	.369729D+01
10	.447521D-02	.123262D+01	.255927D-01	.349808D+01
11	.423528D-02	.125178D+01	.244219D-01	.328836D+01
12	.423188D-02	.125318D+01	.243922D-01	.327542D+01
13	.423188D-02	.125320D+01	.243911D-01	.327519D+01
14	.423188D-02	.125320D+01	.243910D-01	.327518D+01

Dependent variable is RECOV

Source	Sum-of-Squares	df	Mean-Square
Regression	4.708	3	1.569
Residual	0.004	5	0.001
Total	4.713	8	
Mean corrected	1.525	7	

Raw R-square (1-Residual/Total) = 0.999
Mean corrected R-square (1-Residual/Corrected) = 0.997
R(observed vs predicted) square = 0.997

Wald Confidence Interval

Parameter	Estimate	A.S.E.	Param/ASE	Lower < 95%>	Upper
MAX	1.253	0.040	31.344	1.150	1.356
RATE	0.024	0.002	10.683	0.019	0.030
LAG	3.275	0.735	4.457	1.386	5.164

References:

Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol*. 28:126-132.

Fuller B. 2000. A dermal/intravenous cross over study to determine the dermal absorption of [^{14}C]-methamidophos in male rhesus monkeys. Bayer Report No. 109812.

SPSS. 1998. Systat® 8.0. SPSS Inc. Chicago, Illinois.

Thongsinthusak, T., Ross, J. H., Saiz, S. G., and Krieger, R. I. 1999. Estimation of dermal absorption using the exponential saturation model. *Reg. Toxicol. Pharmacol*. 29:37-43.

Wester, R. C., and Maibach, H. I. 1985. *In vivo* percutaneous absorption and decontamination of pesticides in humans. *J. Toxicol. Environ. Hlth*. 16:25-37.

cc: Wendy Zhao
Joseph P. Frank
James Goodbrod

(Dermal/Tamaron-Monkeys; HSM-01007)